REMARKS

Claim Amendments

Claims 24, 26-43, and 45-46, directed to non-elected inventions, have been cancelled without prejudice to or disclaimer of the subject matter therein. Claim 25, directed to the elected invention of Group II and Claims 44 and new Claim 47, directed to the elected invention of Group A, remain. Claim 47 has been added and is supported in the specification on page 4, lines 19-20, and page 4, line 31 to page 5, line 6, for example. As previously stated in the prior response, polyethylene glycol is a cysteine-reactive moiety.

Restriction Requirement

The Examiner has maintained the restriction with respect to Groups I-XIX, and also with respect to Groups A-C. With regard to Groups A-C, Applicants have the following comments. First, the Examiner argues that "each cysteine reactive moiety is distinct from each other", and that "modification with each different moiety will generate distinct IL-11 structural characteristics and biological properties". As noted in the prior response, polyethylene glycol is a cysteine-reactive moiety, and therefore, polyethylene glycol is a proper dependent embodiment of a cysteine-reactive moiety. However, to expedite prosecution, Claims 45 and 46 have been cancelled and Claim 47 has been added as a dependent claim from Claim 44. If the Examiner intends to argue that polyethylene glycol is not a cysteine-reactive moiety, Applicants respectfully request that evidence of this be provided.

Second, Applicants note that the Examiner indicates that Claims 44-46 are withdrawn. This is, however, contrary to the elected subinvention of (A), wherein the cysteine residue is modified with a cysteine-reactive moiety, represented by Claim 44. The Examiner originally required a sub-election among Groups I-XIX of Groups A-C and accordingly, the pending claims under examination should be Claim 25 and Claim 44, as well as new Claim 47, which depends from Claim 44 and is within the scope of elected Claim 44.

Priority Claim

The Examiner contends that the disclosure of the prior filed application, U.S. Patent Application Serial No. 10/400,377 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112, first paragraph, for one or more claims of the present application. Specifically, the Examiner contends that the insertion of a cysteine following the last amino acid of IL-11 is not disclosed in U.S. Application Serial No. 10/400,377 or its parent, U.S. Application Serial No. 09/462,941. Accordingly, the Examiner has denied the benefit of priority to these applications and has assigned a filing date of February 5, 2004.

Applicants respectfully disagree with the Examiner's position that the insertion of a cysteine following the last amino acid of IL-11 is not disclosed in U.S. Application Serial No. 10/400,377 or its parent, U.S. Application Serial No. 09/462,941. To the contrary, the insertion of a cysteine following the last amino acid of IL-11 is explicitly disclosed.

The Examiner is respectfully referred to Example 16 of this application, which is identical to Example 16 of each of U.S. Application Serial No. 10/400,377 and U.S. Application Serial No. 09/462,941, as well as PCT/US98/14497. Example 16, which is directed to cysteine variants of IL-11, at page 53, lines 2-4 expressly states that:

> "Variants in which cysteine residues are added proximal to the first amino acid or distal to the final amino acid of the mature protein are provided."

The addition of a cysteine residue distal to the final amino acid is equivalent to stating the insertion (addition) of a cysteine residue following (distal to) the last amino acid (the final amino acid). Accordingly, the present specification and the applications from which this application claims the benefit of priority under 35 U.S.C. § 120 clearly disclose the presently claimed invention. Moreover, throughout the specification (again, which is identical to that of U.S. Application Serial No. 10/400,377 and U.S. Application Serial No. 09/462,941, as well as PCT/US98/14497), reference to a cysteine being added to the C-terminus of proteins in the growth hormone family is made (see, *e.g.*, page 2, lines 27-28; page 11, lines 17-18). The use of the phrase "following the last amino acid" as compared to "distal to the final amino acid" was originally suggested by the Examiner in U.S. Application No. 09/462,941, as preferred language, but is simply a rephrasing of what the specification clearly teaches ("The subject matter of the

claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement"; MPEP 2163.02). Indeed, the interchangeability of the phrases "proximal to" with "at the beginning of", and "distal to" with "following" is illustrated on page 15, lines 2-4, wherein such phrases are used in this manner with respect to growth hormone, or on page 35, lines 28-30, with respect to erythropoietin. Again, page 53, lines 2-4 clearly disclose this embodiment with respect to IL-11. It is finally noted that original Claim 1 of U.S. Application Serial No. 09/462,941 clearly recites a "cysteine variant of a member of the GH supergene family comprising a cysteine residue...added at the...C-terminus of the proteins."

In view of the foregoing discussion, it is submitted that the present application is fully entitled to the benefit of the complete priority claim as filed with the application.

Rejection of Claim 25 Under 35 U.S.C. §103

The Examiner has rejected Claim 25, contending that this claim is unpatentable over Katre et al. in view of Harmegnies et al. Specifically, the Examiner contends that Kate et al. teach the modification of human IL-2 by substitution of a non-cysteine residue with a cysteine residue, and also that by modifying the IL-2 protein with a cysteine at the end of the molecule allows for attachment of PEG or other polymers at a site that is not necessary for the biological activity of the protein. The Examiner acknowledges that Katre et al. do not teach cysteine mutagenesis of IL-11 and do not teach measuring the biological activity of a variant of IL-11. Harmegnies et al. is cited as teaching that IL-11 is important as a potential therapeutic and that IL-11 can be mutated to increase its therapeutic efficacy. The Examiner contends that it would have been *prima facie* obviousness to generate a cysteine variant of IL-11, wherein a cysteine is inserted following the last amino acid as taught by Katre et al. and measure the activity as taught by Harmegnies et al.

Applicants traverse the rejection of Claim 25 under 35 U.S.C. § 103. Initially, Applicants refer to the discussion of the priority claim above, and contend that the present claims are entitled to the full benefit of the original priority claim, which is July 14, 1997. Accordingly, the reference of Harmegnies et al., having a publication date of 2003, is not available as prior art

against the present claims. As admitted by the Examiner, Katre et al. do not teach cysteine mutagenesis of IL-11 and do not teach measuring the biological activity of a variant of IL-11. Therefore, the remaining reference in the combination fails to teach each and every element of the claimed invention, fail to provide any motivation to modify IL-11, and fail to provide any expectation of success at being able to modify IL-11 in the manner claimed and produce a biologically active IL-11 cysteine variant. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

Moreover, with respect to IL-11, Applicants submit that it was not at all obvious at the time of the invention that the addition of a cysteine following the last amino acid of IL-11 would result in a protein with biological activity. Referring to the publication of Czupryn et al. (*J. Biol. Chem.* 270:978-985, 1995, Applicants' PTO-1449), this reference showed that deleting the last 4 amino acids of IL-11 severely decreased biological activity (25-fold), and deletion of the last 8 amino acids resulted in complete loss of activity (table 1, page 981). Similarly, Miyadi et al. (*Bioscience, Biotechnol. & Biochem.* 60:541-542; Applicants' PTO-1449) showed that deleting a single amino acid from the C-terminus causes a major loss in biological activity (abstract). Accordingly, based on deletion studies available at the time of the invention, it would not be obvious that insertion of a cysteine following the C-terminus of IL-11, or further modification of the protein with a large cysteine-reactive moiety such as PEG, would result in a biologically active protein.

Applicants finally note that cysteine is the only amino acid capable of forming disulfide bonds, so it is unique in its ability to disrupt protein structure. There are many examples in the literature where cysteine modifications result in proteins with poor or no biological activity, likely due to aberrant disulfide bond formation and/or protein dimerization caused by unpaired cysteine residues, which resulted in misfolded species containing inappropriate disulfide linkages, even in regions that otherwise appear to be "unimportant for activity". Therefore, prior to the present invention, wherein the present inventor established rules for the production of biologically active cysteine variants of IL-11 (and other proteins) through protein analysis, laboratory work, and ingenuity, there was no teaching or suggestion where one can modify IL-11 to predictably make biologically active cysteine variants IL-11.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claim 25, and dependent claims thereof, under 35 U.S.C. § 103.

Applicants have attempted to address all of the issues raised by the Examiner in the October 5 office action and submit that the claims are in a condition for allowance. Any remaining concerns regarding these claims should be directed to the below-named agent at (303) 863-9700.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: /Angela Dallas Sebor/
Angela Dallas Sebor
Registration No. 42,460
1560 Broadway, Suite 1200
Denver, CO 80202-5141
(303) 863-9700

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